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Cost-Effectiveness Analysis of Various Pertussis Vaccination Strategies Primarily Aimed at Protecting Infants in the Netherlands

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ABSTRACT

Background: Pertussis is a highly contagious respiratory disease. Despite a high rate of vaccine coverage through the Dutch national immunization program, the incidence of pertussis remains high in the Netherlands and the risk of infection continues. Because pertussis is most severe in unimmunized infants and infants who have only received some of the recommended doses, new pertussis immunization strategies should be considered to protect this vulnerable population.

Objective: This study was designed to estimate the cost-effectiveness of 3 new immunization strategies for possible addition to the current Dutch national immunization program: immunization of the infant at birth, immunization of the parents immediately after birth of the child (cocooning), and maternal immunization during the third trimester of pregnancy.

Methods: A literature search was performed in the PubMed database for articles published in English, German, and Dutch using the following terms: *pertussis*, *whooping cough*, *vaccination strategies*, *maternal immunization*, *cocooning*, *at birth*, *vaccine efficacy*, *mortality*, *underreporting*, *prevalence*, *incidence*, and *cost-effectiveness*. A decision-tree model was developed for this analysis, and data on pertussis morbidity and costs were collected consistently for different age groups (infants <1 year of age and adults 25 to 34 years of age). The size of the infant cohort was set at 200,000 to approximate previous Dutch birth cohorts. The size of the adult cohort was set at 401,380 parents for the cocooning strategy and 201,380 mothers for the maternal immunization strategy. Health benefits (quality-adjusted life-years [QALYs]) and costs were estimated in both cohorts for each of the 3 immunization strate-

gies. Incremental cost-effectiveness ratios were calculated from both a payer's and a societal perspective. The robustness of the results was determined through sensitivity analysis.

Results: In the base-case analysis, cocooning and maternal immunization were found to be effective in reducing the incidence of pertussis among infants (123 and 174 infant cases were expected to be prevented, respectively). Furthermore, cocooning and maternal immunization were estimated to be cost-effective from a payer's perspective (€4600 [US \$6400]/QALY and €3500 [\$4900]/QALY, respectively) and even cost-saving from a societal perspective (savings of up to €7200 [\$10,100] and €5000 [\$7000], respectively). Sensitivity analyses revealed that favorable cost-effectiveness was generally robust. In the sensitivity analysis, the cost-effectiveness of cocooning and maternal immunization was mostly sensitive for changes in assumptions on underreporting (200-fold increase in reported number of symptomatic cases) of pertussis disease and infection. With no underreporting, the ICER was estimated at €211,900 (\$296,700)/QALY for cocooning and €81,600 (\$114,200)/QALY for maternal immunization from a payer's perspective. However, even at much lower levels of underreporting (20- to 30-fold increase in incidence), cost-effectiveness remained favorable. The cost-effectiveness of the third strategy, at-birth immunization,

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was highly unfavorable (€329,900 [\$461,900]/QALY from a payer's perspective and €330,100 [\$462,100]/QALY from a societal perspective).

Conclusions: This study estimated that the addition of cocooning or maternal immunization to the current Dutch national immunization program likely would be cost-effective or even cost-saving. These estimates were mainly due to reduction in the number of cases among parents, which are likely to be mild and therefore would largely remain unreported. Immunization at birth was not a cost-effective strategy. Cocooning was the most expensive intervention to implement; however, it resulted in the highest number of QALYs gained (mainly in adults). Maternal immunization would offer better protection of infants, due to maternally acquired antibodies. (*Clin Ther.* 2010;32:1479–1495) © 2010 Excerpta Medica Inc.

Key words: pertussis, cost-effectiveness, immunization, cocooning, maternal, booster.

INTRODUCTION

Pertussis is a highly contagious respiratory disease caused by the bacteria *Bordetella pertussis* and occasionally *B parapertussis*.¹ Transmission occurs primarily through contact with respiratory droplets or secretions from infected persons.² Pertussis infection in adolescents and adults is generally mild and passes unnoticed³; as a consequence, pertussis is highly underreported in these age groups.^{3,4} However, pertussis infection is severe in infants, in whom it can cause serious morbidity and even death.⁵ Pertussis vaccination programs have been implemented, but unvaccinated infants, partly vaccinated infants (ie, those who have received only some of the recommended doses), and individuals from groups that refuse vaccination for various reasons (including religious beliefs) remain at risk.

Implementation of childhood immunization programs has greatly reduced the burden of pertussis among infants and young children worldwide; ~760,000 deaths worldwide are prevented annually.⁶ However, the incidence among adolescents and adults remains high (eg, 0.1–200 cases per 100,000), and cases of pertussis in these groups are important sources of infection for unvaccinated and partly vaccinated infants.^{7–11} Approximately 150,000 cases of pertussis are reported annually by the World Health Organization.¹² To reduce transmission of the bacteria in the general population, some countries (eg, France, Australia) have already

implemented pertussis immunization programs for adolescents.^{12,13} Other immunization strategies, such as universal adult immunization and immunization of “new” fathers and mothers, also have been proposed in the literature to further reduce the incidence of pertussis among infants.⁶

In the Netherlands, infants have been immunized against pertussis routinely since 1953, resulting in a rapid decrease in the incidence and mortality of the disease (eg, a 5-fold decrease in pertussis mortality was observed during the period 1953–1958).¹⁴ The current infant pertussis vaccination schedule consists of 3 doses of the vaccine at 2, 3, and 4 months of age and 2 booster vaccinations at 11 months and 4 years of age.¹⁵ The Dutch national immunization program has reported coverage of ~96% of the population.

Despite these efforts, the incidence of pertussis in adolescents and adults has increased during the past decade; an increase (~2-fold) was seen in these age groups during the period 2006 to 2008.^{16,17} It has been suggested that vaccine-induced immunity wanes after ~4 to 12 years.¹⁸ Introduction of the additional booster vaccination at the age of 4 years in 2001 has led to a significant reduction in pertussis cases among children 4 to 10 years of age.¹⁵ However, mainly due to waning immunity, the incidence among adolescents and adults remains high. This is a cause for concern because parents potentially represent an important source of transmission of pertussis to their infants with increased risks for severe disease.^{10,19,20} Therefore, additional pertussis immunization strategies should be considered to protect and reduce the incidence of pertussis among this population.

This article investigates 3 such strategies: vaccination of the infant at birth, vaccination of both parents immediately after birth of the child (cocooning), and vaccination of the mother in the third trimester of pregnancy (maternal immunization). Clinical trials have been performed to estimate the effectiveness and tolerability of vaccinating adults and the immunogenicity and tolerability of at-birth immunization; however, no clinical trials in pregnant women have been published.^{21–24} Currently, only the cocooning strategy could be implemented because no vaccine has yet been licensed for use in newborns or pregnant women.

If clinically effective, immunization at birth could be an attractive strategy because it would directly increase the protection of the most vulnerable group against pertussis and could therefore significantly lower the

burden of the disease.^{23–25} However, because of the delay between immunization and vaccine-induced immunity (discussed in the next section), immunization at birth will never provide protection immediately after birth.^{24,26}

Because mothers have been identified as the most important source of infection, immunization of mothers during pregnancy (maternal immunization) may considerably reduce pertussis transmission to newborns. Furthermore, infants might be protected by antibodies acquired from the mother (immunoglobulin G). However, there might be reluctance to implement maternal immunization because of safety concerns for the unborn child. Another feasible strategy would be immunization of both parents during pregnancy or immediately after delivery to protect infants from the 2 main sources of infection (cocooning).^{10,26–29} The latter approach might eliminate concerns about the safety of the immunization strategy and might therefore be more acceptable.

Before implementing any vaccination strategy, it is important to determine the cost-effectiveness of the intervention. The aim of this study was to estimate the cost-effectiveness of each of the 3 vaccination strategies—immunization at birth, cocooning, and maternal immunization—as potential additions to the current immunization program in the Netherlands.

PATIENTS AND METHODS

A literature search was performed in the PubMed database for articles published in English, German, and Dutch using the following terms: *pertussis*, *whooping cough*, *vaccination strategies*, *maternal immunization*, *cocooning*, *at birth*, *vaccine efficacy*, *mortality*, *under-reporting*, *prevalence*, *incidence*, and *cost-effectiveness*. Articles were selected on the basis of relevance. Articles publishing Dutch data were preferred; if unavailable, articles publishing data from other western countries were used. A decision-analytic model was designed to estimate the incremental cost-effectiveness ratio (ICER) of adding one of these immunization strategies to the current immunization program. Each strategy was compared with the current Dutch pertussis vaccination schedule (5 doses) using an acellular pertussis vaccine. Furthermore, a direct comparison of costs and health gains was made between the different strategies. In accordance with the Dutch guidelines, future health outcomes and costs were discounted at rates of 1.5% and 4.0%, respectively.³⁰ As a benchmark, an intervention was considered to be cost-effective if the ICER was

<€20,000 (US \$28,000) per quality-adjusted life-year (QALY) from a societal perspective.³¹

Vaccination Strategies

For immunization at birth, it was assumed that protection was not achieved until 2 weeks after administration of the first vaccine dose.³² For subsequent doses at 2, 3, and 4 months of age, vaccine effectiveness was immediately increased to the respective higher levels. Because no Phase III studies in this age group have yet been published, vaccine effectiveness was extrapolated from Dutch incidence data and Swedish and US follow-up studies.^{33,34} Based on the Dutch incidence data, it was estimated that the vaccine effectiveness after administration of the first, second, and third doses would be ~40%, 70%, and 89%, respectively. These effectiveness estimates are consistent with previous observational studies in which the vaccine effectiveness was estimated at ~30% to 50% after the first dose. Therefore, a maximum vaccine effectiveness of 89% was assumed after administration of the third dose of 4 doses at 3 months of age. It was also assumed that the fourth dose did not further increase the vaccine effectiveness. Therefore, after 4 months, the vaccination program already in place was assumed to provide the maximum degree of protection, with the fourth dose effectively prolonging the duration of protection to the maximum assumed.

For the cocooning strategy, it was assumed that fathers would be vaccinated during the pregnancy and mothers would be vaccinated immediately after delivery. In terms of transmitting pertussis from the mother to the infant, a delay of 2 weeks was assumed to achieve full effectiveness of the vaccine in the mother. Implementation of this strategy was assumed to reduce the incidence of pertussis among both the vaccinated adults and their newborns. In adults, a vaccine effectiveness of 89% was assumed.^{18,22} In the Netherlands, mothers and fathers were estimated to be the source of infection in ~38% and 17% of infant cases of pertussis, respectively; therefore, effectiveness in infants was set at 49% (ie, $[38 + 17] \times .89$).^{8,17,35} Because of the 2-week delay in achieving full effectiveness in the mother, infants (during the first 2 weeks of life) were assumed to only be protected from transmission of the disease from the father.

For the maternal immunization strategy, it was assumed that mothers were vaccinated during the third trimester of pregnancy and that the effectiveness of the immunization would be 89% (in both the mother and

the newborn).²² The unborn child was assumed to acquire protective maternal antibodies and, therefore, may be protected immediately after birth, both by the antibodies and as a consequence of reduced risk of transmission from the mother.^{36–42} Protection provided by maternally acquired antibodies in infants was assumed to last 4 months,⁴³ which bridged the gap to where protection was assumed from the immunization program already in place. Furthermore, it was assumed that, because of the rapid decrease in antibody titers after 6 to 12 months, the vaccination only protected the infant of the current pregnancy.

In all 3 strategies, vaccine-induced protection against disease was assumed to last 8 years in adults.¹⁸ With a possible duration of protection for infection being much shorter (~2 years) and the optimal interval of revaccination still being investigated, the calculations for both cocooning and maternal immunization should be considered to apply to first pregnancies only.

Model

A decision-tree model (Figure 1) was developed to estimate the expected costs, savings, and health gains

of the 3 immunization strategies. Because adverse events due to acellular pertussis vaccine are uncommon (eg, incidence of fever $>37.5^{\circ}\text{C}$ [99.5°F], 5.5%–8.0% of recipients) and generally mild (eg, incidence of severe [grade 3] symptoms, 2.5%–2.8%), associated QALY losses and costs were not included in the analysis.^{13,44,45} The decision tree was constructed in TreeAge Data Pro™, version 4.0 (TreeAge Software Inc., Williamstown, Massachusetts).

Costs, savings, and health gains were calculated over an 8-year period (matching the assumed duration of protection in adults) in the 2 cohorts simultaneously: infants <1 year of age and adults 25 to 34 years of age. The size of the infant cohort was set at 200,000 to approximate previous Dutch birth cohorts. The size of the adult cohort was set at 401,380 parents for the cocooning strategy and 201,380 mothers for the maternal immunization strategy. These cohort sizes included the risk of spontaneous abortions in the model, next to numbers of parents in line with the assumed infant cohort size.⁴⁶ Immunization at birth was assumed to affect only the cohort of newborns, whereas cocooning and maternal immunization were assumed to affect

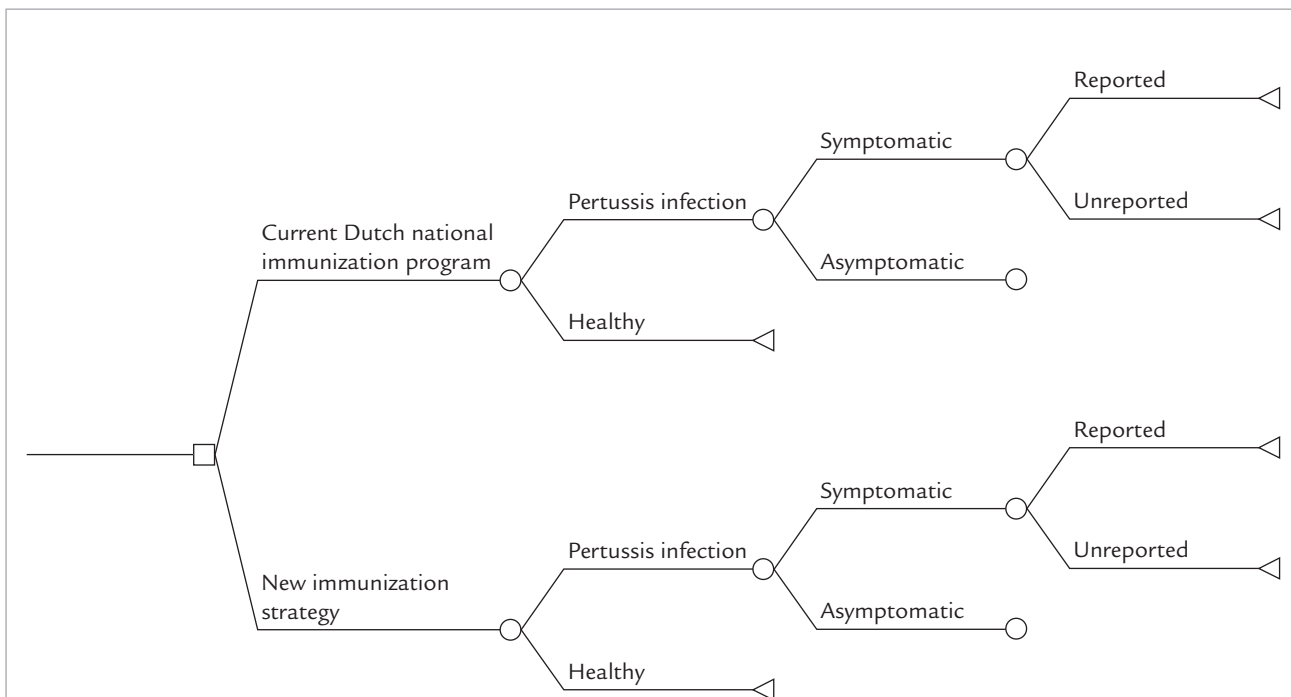


Figure 1. Generic decision tree used for calculation of the cost-effectiveness of potential pertussis immunization strategies.

both cohorts (adults and newborns). Two models were designed for both cohorts (adults and infants) separately, which meant that no direct relation existed between the number of adult and infant cases. Therefore, increasing the incidence of pertussis in adults to correct for underreporting did not result in a corresponding increase in cases in infants. The efficacy of an adult immunization strategy (eg, cocooning or maternal immunization) was modeled in the infant cohort by reducing the risk of disease by the efficacy of maternally acquired antibodies and/or by reduced transmission from the parents.

For the analysis of cost-effectiveness, the cohorts in the various immunization strategies were assumed to be fully protected by vaccination, based on the current vaccination coverage of the Dutch national immunization program (96%). A lower rate of vaccine coverage would not change the cost-effectiveness results, but it would affect the number of cases averted and any budget-consequence calculations potentially linked to the cost-effectiveness analysis.

Incidence, Hospitalization, and Mortality Data

Parameter values used in the model were obtained from the literature, national databases, and expert opinions. Because fluctuations in the incidence of pertussis occur annually, the mean incidence over a period of several years was calculated. In particular, the 2002 to 2005 age-specific pertussis incidence data were obtained from the mandatory notifications to the Centre for Infectious Disease Control of the Dutch National Institute for Public Health and the Environment (Bilthoven, the Netherlands). It is generally accepted that notifications of pertussis disease do not capture all cases of disease and infection; therefore, incidence data were corrected for underreporting.^{4,47–50} For the Netherlands, it has been estimated that the incidence of infection was 6.6% per year in 1995 and 1996.⁴ Using a dynamic transmission model and age-specific data on underreporting,⁴ de Vries et al⁵¹ estimated that the total number of symptomatic pertussis cases (reported and unreported) in adults is ~200-fold higher than reported (95% CI, 110–292), resulting in an annual symptomatic pertussis incidence of ~3.5% in the adult population.

Given that some of the previously defined strategies were gender specific, the incidence data were analyzed for men and women separately, if relevant. For the youngest group (0–5 months of age), the annual number of hospital admissions was used to estimate the yearly incidence of pertussis, which appeared to be slightly

higher than the number of reported cases in that age group. Pertussis in infants is generally severe and therefore likely to be reported; hence, it was assumed conservatively that no further underreporting occurred in this age group. Data on pertussis-related hospitalizations and admissions to the intensive-care unit were obtained from 2 Dutch hospital databases—Prismant (Utrecht, the Netherlands) and Pediatric Intensive Care Unit (Rotterdam, the Netherlands), respectively.

In the period 1998 to 2005, five pertussis-related deaths were reported among infants (all were 0 to 3 months of age).^{15,46} The mortality risk was calculated from these data. An overview of the pertussis incidence and hospitalization data used in the base-case analysis is presented in **Table I**.^{52,53}

Utilities

Lee et al^{54,55} estimated that the quality of life during pertussis disease for infants and adults decreased to 0.58 and 0.85, respectively. Assuming a mean disease duration of 3 months for infant and reported adult cases of pertussis, the QALY losses were estimated at 0.10 and 0.04 for infants and adults, respectively. A QALY loss of 0.02 was assumed for unreported symptomatic adult cases of pertussis.

Costs of Illness

For the estimation of disease-related costs, distinctions were made between reported and unreported symptomatic cases of pertussis. Direct and indirect costs were included, and national unit costs were obtained from Oostenbrink et al,⁵⁶ reflecting the guideline prices to be used in Dutch health economic/pharmacoeconomic analyses. All costs were reported in euros (€s) at 2008 price levels (2008 conversion factor: €1.00 ≈ \$1.40; US \$ rounded to nearest hundred).

The direct costs of reported pertussis cases included all costs associated with diagnostics, visits to a general practitioner (GP), antibiotic treatments, and hospitalizations. In the analysis, it was assumed that all infants were treated in the hospital on an ambulatory basis, with 1 GP visit and 3 specialist visits (expert panel). For reported adult cases, 2 GP visits were assumed.^{57,58} For cases treated in the hospital, several diagnostic tests were included (polymerase chain reaction [PCR], serology, C-reactive protein, chest radiography, and blood concentration assessment). For the adults treated by a GP, pertussis was assumed to be diagnosed using culture, PCR, or serology. Serology was the most frequently

Table I. Mean pertussis incidence and hospitalization data (2002–2005) used in the base-case analysis.

Age Group	No. of Reported Cases*	No. of Hospital Admissions ^{52,53}	Length of Stay, Days	Costs Per Stay, € (US \$) [†]
Infants, months [‡]				
0	18.0	18.0	10.2	6644 (9302)
1	55.3	55.3	10.3	5450 (7630)
2	46.8	46.8	6.2	3394 (4752)
3	28.8	28.8	8.1	3556 (4978)
4	13.8	13.8	6.4	2482 (3475)
5	7.0	7.0	5.8	2249 (3149)
6	20.1	8.3	6.1	2595 (3633)
7	10.9	4.5	3.8	1932 (2705)
8	20.6	8.5	6.0	2327 (3258)
9	14.1	5.8	6.9	2675 (3745)
10	12.9	5.3	2.7	1046 (1464)
11	9.7	4.0	3.1	1202 (1683)
Adults [§]	358.0	0.7	3.4	1542 (2159)

*Estimates for infants 0 to 5 months of age were based on reported hospitalizations for this age group.

[†] 2008 Pricing; includes costs of normal and intensive-care admissions (2008 conversion factor: €1.00 ≈ US \$1.40).

[‡] Cohort of 200,000 infants <1 year of age.

[§] Cohort of 2,000,000 adults 25 to 34 years of age.

used test (83% of diagnosed cases).⁵⁹ Hospitalization costs were calculated from the annual number and duration of hospital admissions (standard and intensive care) (Table I).^{52,53} Annually, ~4% of infant cases were assumed to be treated for 7 to 13 days in the intensive-care unit.⁵³ Finally, it was assumed that only reported cases of pertussis were treated with azithromycin. Because of the lack of data, it was assumed conservatively that unreported cases incurred no medical costs. An overview of the costs per pertussis infection is provided in Table II.

Indirect costs consisted of the costs associated with loss of productivity by parents who stayed home to care for their pertussis-infected child or because they had pertussis themselves. In the Netherlands in general, mothers have 3 months of maternity leave after delivery; therefore, it was assumed that no indirect costs were incurred for infants aged 0 to 2 months. For older children, a loss of 10 work days for the mother was assumed.⁶⁰ For reported and unreported symptomatic adult cases, losses of 5 and 2.5 days for a pertussis infection were assumed, respectively.^{61,62} Using the friction-costing method, mean indirect costs of €80.69 (\$112.97) and €50.76 (\$71.06) per day were assumed for males and females, respectively.^{56,63}

Vaccination Costs

For vaccination, the costs of the vaccine itself and administration were included in the analyses. The price for the acellular pertussis vaccine was set at €18.30 (\$25.60) (corresponding to the retail price in 2008).⁶⁴ Based on a recently published cost-effectiveness analysis of vaccination against human papillomavirus, the vaccine administration cost was assumed at €6.00 (\$8.40).⁶⁵ Thus, the total immunization cost of a new pertussis vaccination strategy was assumed to be €24.30 (\$33.40) per dose. For the at-birth immunization strategy, vaccination costs might be lower because midwives are already present during birth and administration might be relatively easy. Lower vaccination prices were investigated in sensitivity analyses.

Sensitivity Analyses

For the calculation of the base-case cost-effectiveness of the 3 immunization strategies, uncertainty concerning vaccine effectiveness, QALY losses, and underreporting was taken into account in a probabilistic sensitivity analysis (PSA). In the PSA, a β -distribution for vaccine effectiveness ($\alpha = 1.2$, $\beta = 0.15$),²² triangle distributions for QALY losses in infants (lower limit, 0.15; mode,

Table II. Estimated direct and indirect pertussis-related costs per pertussis infection.

Variable	Ambulatory Cases Treated in Hospital, € (US \$)	Cases Treated by General Practitioner, € (US \$)
Direct costs		
Diagnostics	221.83 (310.56)	52.48 (73.47)
Visits to general practitioner	22.59 (31.63)	45.18 (63.25)
Visits to specialist	158.67 (222.14)	0
Treatment*	9.40 (13.16), infant 17.24 (24.14), adult	9.40 (13.16), infant 17.24 (24.14), adult
Indirect costs†		
Infants‡	508.00 (711.20)	508.00 (711.20)
Adult female, reported	254.00 (355.60)	254.00 (355.60)
Adult male, reported	403.00 (564.20)	403.00 (564.20)
Adult female, unreported	127.00 (177.80)	127.00 (177.80)
Adult male, unreported	202.00 (282.80)	202.00 (282.80)

*2008 Pricing; it was assumed that adult cases were treated with cough medicines in addition to antibiotics (2008 conversion factor: €1.00 ≈ US \$1.40).

† Cohort of 200,000 infants <1 year of age and cohort of 401,380 adults 25 to 34 years of age.

‡ Work days lost by parents caring for their ill child.

0.10; upper limit, 0.05), reported adults (lower limit, 0.06; mode, 0.04; upper limit, 0.02), and unreported adults (lower limit, 0.04; mode, 0.02; upper limit, 0.001) and a normal distribution for the underreporting factor (mean [SD], 200 [54]) were applied.

Deterministic univariate sensitivity analyses were conducted on QALY losses, vaccine costs, indirect costs, pertussis transmission rates, vaccine effectiveness, and the underreporting factor. For example, the number of work days lost by the mother of an infant with pertussis was decreased from 10 to 5 days.^{32,57,61,66} Furthermore, additional indirect costs for infants 0 to 2 months of age were included, assuming that the father might also stay at home to care for the infant. Vaccination costs up to €30.00 (\$42.00) and reduced to €18.00 (\$25.20) were investigated. Finally, the QALY loss for infants was increased from 0.1 to 0.2.

For industrialized countries, parents appeared to be the source of infection in ~50% of cases, which is consistent with findings in the Netherlands.^{10,19} Because the infants remained susceptible to other pertussis sources, the sensitivity analyses tested the scenario excluding benefits in infants, leaving only the benefits of parents for the cocooning and maternal immunization strategies. Furthermore, the impact of vaccine ef-

fectiveness on the outcomes was assessed by decreasing vaccine effectiveness by 20% to cope with uncertainty, in particular related to maternal immunization and immunization at birth, in the absence of formal clinical trials.^{32,66} The specific impact of the effectiveness of maternally acquired antibodies also was investigated. For that purpose, effectiveness in infants was decreased from 89% to 70%. Finally, the QALY losses of unreported adult cases were decreased stepwise from 0.02 to zero.

In the previously mentioned part of the sensitivity analysis, the underreporting factor remained fixed at 200, as in the base-case analysis (ie, adult symptomatic pertussis incidence was considered to be increased 200-fold from reported cases in all sensitivity analyses). In the second part of the sensitivity analysis, the adjusted incidence data were decreased stepwise in the adult cohort (lowering the underreporting factor). The lower limit for the adult pertussis incidence was the number of reported cases. For the infant cohort, the incidence was increased 3-fold compared with the hospitalizations reported in the base case, as reported in a study by Crowcroft et al,⁴⁹ which estimated that pertussis mortality was underestimated 3-fold in England. Because mortality was modeled as a function of inci-

dence, varying the incidence simultaneously changed the mortality rate.

RESULTS

Base-Case Analysis

The annual numbers of symptomatic pertussis cases (reported and unreported) in infants <1 year of age and adults 25 to 34 years of age were estimated at 258 and 114,955, respectively. After correcting the incidence data for underreporting, the total number of adult cases was 200-fold higher than the number of reported cases alone (Table I). In the Netherlands, the total pertussis-related costs for both cohorts combined were estimated at €971,000 (\$1,359,400) and €14,781,900 (\$20,694,700) annually from the payer and societal perspectives, respectively. Pertussis costs per case for infants ranged from €660 (\$900) for infants 11 months of age to €7060 (\$9900) for infants 0 months of age. Implementation of each of the investigated immunization strategies resulted in a decrease in pertussis incidence among infants and/or adults (Table III). Maternal immunization appeared to be the most effective strategy in protecting infants against pertussis. At-birth immunization did not appear to be an attractive alternative because only a small number of cases among infants and no cases among adults would be prevented. Cocooning appeared to be an attractive alternative to maternal immunization, although fewer infant pertussis cases would be prevented.

The ICERs estimated for adding each of the proposed immunization strategies to the current Dutch national immunization program from the payer and societal perspectives are presented in Table IV. The incremental costs reflected the differences between the total costs of a potential pertussis vaccination strategy (disease and vaccination costs) and the costs under the current program (only disease costs considered). The 95% CIs represented the range of the ICERs by taking into account all uncertainties in underreporting, vaccine effectiveness, and QALY losses using the PSA.

From the payer's perspective, the cost-effectiveness of cocooning and maternal immunization were estimated to be similar, with ICERs of €4600 (\$6400)/QALY (95% CI, €2200–€17,800 [\$3100–\$24,900]) and €3500 (\$4900)/QALY (95% CI, €1700–€15,000 [\$2400–\$21,000]), respectively (Table IV). Conversely, immunization at birth was not cost-effective. When directly comparing cocooning with maternal immunization, cocooning was estimated to be cost-effective, with an

Table III. Estimated number of pertussis cases averted with the investigated immunization strategies compared with the current Dutch national immunization program.

Strategy	No. of Cases Averted		
	Infants*	Adults†	Total (95% CI)‡
At-birth immunization	55	NA	55 (18–62)
Cocooning§	123	102,259	102,382 (35,399–159,552)
Maternal immunization	174	59,089	59,263 (20,480–92,510)

NA = not applicable.

* Cohort of 200,000 infants <1 year of age.

† Cohort of 401,380 adults 25 to 34 years of age.

‡ 95% CIs included uncertainty on underreporting, vaccine effectiveness, and quality-adjusted life-year losses.

§ For cocooning, the cohort size was set at 401,380.

|| For maternal immunization, the cohort size was set at 201,380.

ICER of €6300 (\$8800)/QALY. Excluding unreported symptomatic cases from our analysis (eg, assuming no underreporting) resulted in a significant increase in the estimated ICER for both immunization strategies (cocooning, €211,900 [\$296,700]/QALY; maternal immunization, €81,600 [\$114,200]/QALY).

From the societal perspective, cocooning and maternal immunization were estimated to be cost-saving, with savings of up to €7200 (\$10,100) and €5000 (\$7000) per QALY gained, respectively. For immunization at birth, little difference was found between the payer and societal perspectives because it was assumed that no indirect costs would be incurred for infants 0 to 2 months of age. The small differences between payer and societal perspectives were due only to chance in the uncertainty analysis. Finally, when both parents were vaccinated during the pregnancy, an ICER of €4400 (\$6200)/QALY was found from the payer's perspective.

Deterministic Sensitivity Analysis

The results of the sensitivity analyses from the payer's perspective are presented in Table V. For immunization

Table IV. Comparison of base-case estimates of incremental costs and benefits of the investigated immunization strategies with the current Dutch national immunization program from the payer and societal perspectives.

Strategy	Incremental Costs (95% CI)*	QALYs Gained (95% CI)*	ICER/QALY Gained (95% CI)*
Payer's perspective			
At-birth immunization	€4,531,300 (€4,712,800 to €4,799,800) \$6,343,800 (\$6,597,900 to \$6,719,700)	13.7 (4.4 to 13.1)	€329,900 (€256,900 to €1,071,400) \$461,900 (\$359,700 to \$1,500,000)
Cocooning	€9,140,000 (€9,082,000 to €9,393,000) \$12,796,000 (\$12,714,800 to \$13,150,200)	1975 (438 to 3805)	€4600 (€2200 to €17,800) \$6400 (\$3100 to \$24,900)
Maternal immunization	€4,053,100 (€3,982,400 to €4,456,300) \$5,674,300 (\$5,575,400 to \$6,238,800)	1166 (282 to 2326)	€3500 (€1700 to €15,000) \$4900 (\$2400 to \$21,000)
Societal perspective			
At-birth immunization	€4,534,100 (€4,566,700 to €4,711,700) \$6,347,700 (\$6,393,400 to \$6,596,400)	13.7 (4.4 to 13.1)	€330,100 (€256,900 to €1,071,600) \$462,100 (\$359,700 to \$1,500,200)
Cocooning	-€5,212,300 (-€13,263,200 to €4,384,800) -\$7,297,200 (-\$18,568,500 to \$6,138,700)	1975 (447 to 4002)	CS: UL = €7200 CS: UL = \$10,100
Maternal immunization	-€2,580,200 (-€6,284,600 to €1,999,600) -\$3,612,300 (-\$8,798,400 to \$2,799,400)	1166 (280 to 2336)	CS: UL = €5000 CS: UL = \$7000

QALY = quality-adjusted life-year; ICER = incremental cost-effectiveness ratio; CS = cost-saving; UL = upper limit of 95% CI.
 *2008 Pricing; 95% CI includes uncertainty on underreporting, vaccine effectiveness, and QALY losses (2008 conversion factor: €1.00 ≈ US \$1.40).

at birth, all parameters in the sensitivity analyses had a relevant impact on the ICER. However, in all scenarios analyzed, the ICER of at-birth immunization remained higher than the informal Dutch threshold of €20,000 (\$28,000)/QALY.

For cocooning and maternal immunization, the estimated ICERs seemed to be robust. The ICERs varied little with changes in QALY loss, indirect cost, vaccine cost, and transmission rate. Slight variation was esti-

mated when the vaccine effectiveness was changed. Even in that case, the ICER remained under the threshold of €20,000 (\$28,000)/QALY.

In Table V, outcomes were only shown from the payer's perspective. From the societal perspective, cocooning and maternal immunization were cost-saving, and ICERs are meaningless in such situations. For immunization at birth, no differences between the payer and societal perspectives were found in the analysis.

Table V. Results of the sensitivity analysis on the incremental cost-effectiveness ratio (ICER) for the immunization strategies analyzed from the payer's perspective.

Variable	ICER/QALY (95% CI)*		
	At-Birth Immunization	Cocooning	Maternal Immunization
Base case	€329,900 (€256,900–€1,071,400) \$461,900 (\$359,700–\$1,500,000)	€4600 (€2300–€20,600) \$6400 (\$3200–\$28,800)	€3500 (€1700–€15,000) \$4900 (\$2400–\$21,000)
QALY loss, 0.2 in infants [†]	€236,300 (€204,900–€751,300) \$330,800 (\$286,900–\$1,051,800)	€4600 (€2300–€19,400) \$6400 (\$3200–\$27,200)	€3400 (€1700–€14,600) \$4800 (\$2400–\$20,400)
No administration cost (€18.00 [\$25.20])	€242,500 (€188,300–€781,600) \$339,500 (\$263,600–\$1,094,200)	€3400 (€1700–€15,400) \$4800 (\$2400–\$21,600)	€2400 (€1200–€10,900) \$3400 (\$1700–\$15,300)
Increased vaccine cost (€30.00 [\$42.00])	€417,200 (€325,500–€1,327,800) \$584,100 (\$455,700–\$1,858,900)	€5800 (€2800–€26,300) \$8100 (\$3900–\$36,800)	€4500 (€2300–€20,000) \$6300 (\$3200–\$28,000)
No transmission from mother or father to child (0%)	NA	€4900 (€2400–€22,700) \$6900 (\$3400–\$31,800)	€3600 (€1800–€15,700) \$5000 (\$2500–\$22,000)
3-Fold increased incidence in mortality in infants	€162,000 (€115,200–€579,000) \$226,800 (\$161,300–\$810,600)	€4310 (€2200–€18,500) \$6000 (\$3100–\$25,900)	€2200 (€1000–€10,700) \$3100 (\$1400–\$15,000)
Decreased effectiveness, maternal antibodies (70%)	NA	NA	€3600 (€1800–€15,100) \$5000 (\$2500–\$21,100)
Decreased vaccine effectiveness [‡]	€1,392,100 (€507,200–€2,230,600) \$1,948,900 (\$710,100–\$3,122,800)	€6100 (€3200–€19,600) \$8500 (\$4500–\$27,400)	€4600 (€2500–€14,100) \$6400 (\$3500–\$19,700)
Excluding unreported cases from analysis	NA	€211,900 (€161,700–€511,700) \$296,700 (\$226,400–\$716,400)	€81,600 (€65,600–€186,700) \$114,200 (\$91,800–\$261,400)

QALY = quality-adjusted life-year; NA = not applicable.

*The ICER (2008 pricing) reflects the net costs per QALY gained compared with the current Dutch national immunization program; 95% CI includes uncertainty on underreporting, vaccine effectiveness, and QALY losses (2008 conversion factor: €1.00 ≈ US \$1.40).

[†] Parameters excluded in probabilistic sensitivity analysis.

[‡] Vaccine effectiveness was 20% lower than that of the base case.

Specific Sensitivity Analysis for Underreporting

The ICER of pertussis immunization may be sensitive to the assumptions made about the magnitude of underreporting and the utility loss of unreported cases. Further sensitivity analyses of these aspects are presented in this section.

In the base-case analysis, an estimated underreporting of symptomatic pertussis (incidence 200-fold greater than reported cases) was taken into account for adults. The ICERs of cocooning and maternal immunization for different underreporting levels/incidence data in both the payer and societal perspectives are presented in **Figure 2**. It appeared that the ICERs for both immunization strategies were highly sensitive to the number of unreported symptomatic pertussis cases. When the incidence was decreased to the number of reported cases only, both strategies were associated with unfavorable ICERs. However, by decreasing the incidence of symptomatic pertussis (lowering the underreporting factor),

the ICER increased slowly. For these 2 strategies, an 80% to 90% decrease in incidence or underreporting factor still resulted in ICERs that would be considered favorable in terms of the informal Dutch threshold for cost-effectiveness from the societal perspective. Almost no difference was found between the payer and societal perspectives when the underreporting factor became relatively low.

In the base-case analysis, the assumed QALY loss for unreported cases was 0.02. Because the exact QALY loss in these cases was unknown, the value was decreased stepwise from the base case (**Figure 3**). The ICER appeared to be sensitive for the assumptions on QALY losses in the unreported pertussis cases. However, when QALY losses approached zero for unreported cases, the ICERs increased to possibly unacceptable levels for both cocooning and maternal immunization from the payer's perspective. From the societal perspective, both strategies remained cost-saving, independent of QALY loss

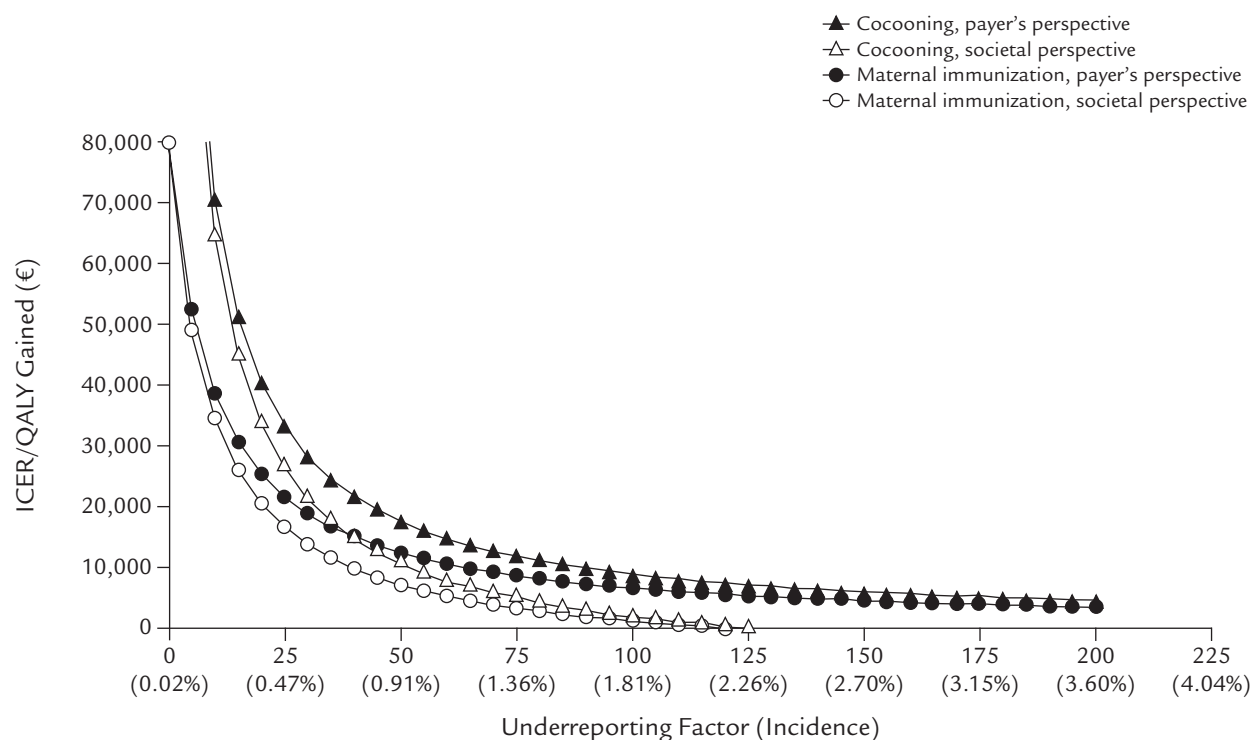


Figure 2. Sensitivity analyses of the cocooning and maternal immunization strategies, showing the impact of changes in the incidence of pertussis among adults on the incremental cost-effectiveness ratio (ICER) per quality-adjusted life-year (QALY) of the 2 strategies. The horizontal axis shows the correction factors for underreporting among adults (percentages in parentheses reflect the estimated incidence after correcting for underreporting). (2008 Conversion factor: €1.00 ≈ US \$1.40.)

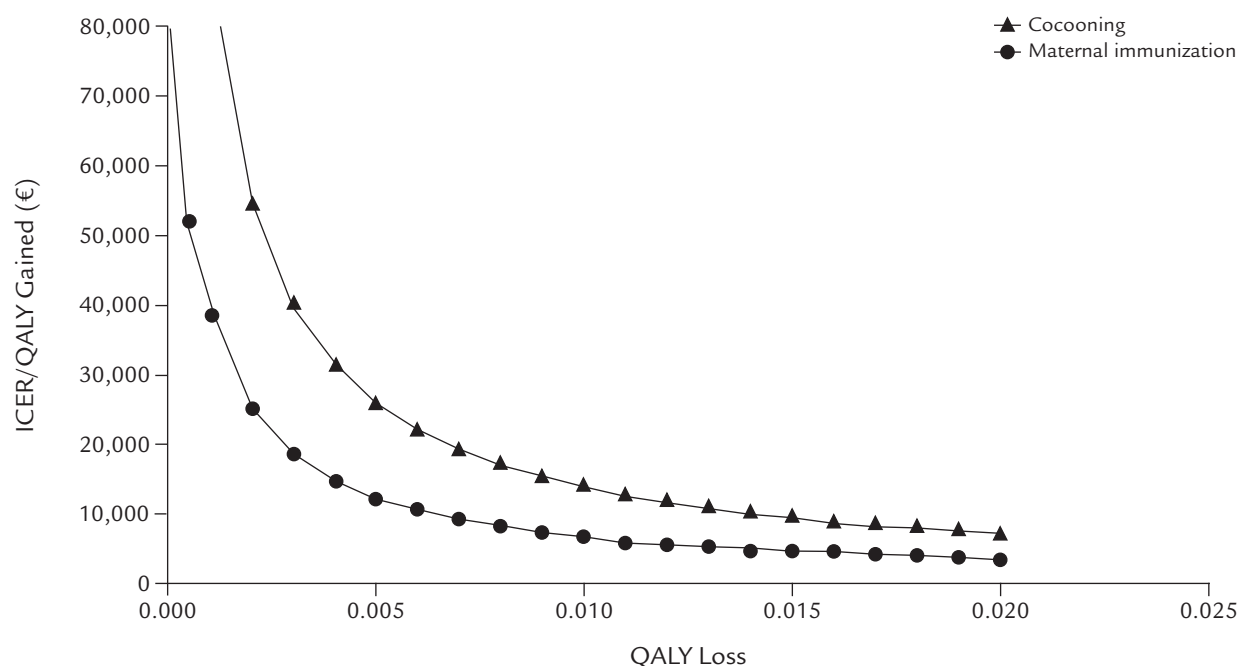


Figure 3. Sensitivity analyses of the cocooning and maternal immunization strategies showing the impact of quality-adjusted life-year (QALY) losses among unreported adult cases of pertussis on the estimated incremental cost-effectiveness ratio (ICER) from the payer's perspective. (2008 Conversion factor: €1.00 ≈ US \$1.40.)

(data not shown because the absolute negative values of ICERs are meaningless).

DISCUSSION

This study estimated the cost-effectiveness of adding new pertussis immunization strategies to the current Dutch national immunization program. In particular, the strategies of immunization at birth, cocooning, and maternal immunization were investigated. The introduction of a new pertussis immunization strategy should primarily be aimed at reducing the incidence among infants; however, benefits in other age groups also should be considered. To our knowledge, this is the first consistent comparison of 3 relevant strategies that can be considered to further reduce the incidence of pertussis.

In the base-case analysis, it was estimated that maternal immunization might be the most effective strategy in preventing pertussis in infants. Because of the assumed limited vaccine effectiveness in infants, immunization at birth did not appear to be as effective. By saving more QALYs, cocooning was estimated as an attractive al-

ternative to maternal immunization, although ~30% fewer infant pertussis cases might be prevented. Both cocooning and maternal immunization would be similarly and highly cost-effective according to the informal Dutch threshold for cost-effectiveness.³¹ Immunization at birth was estimated not to be cost-effective.

These cost estimates are consistent with those reported by de Greeff et al⁵⁸ for the Netherlands and those reported by Lee et al⁶⁷ in their analysis of pertussis immunization in Germany, for both infant and adult cases. In particular, de Greeff et al recently calculated pertussis-related costs for 5 age groups (<1 year, 1–9 years, 10–19 years, 20–44 years, and ≥45 years) in the Netherlands. In the present study, pertussis costs were calculated using other data sources and more detail for costs among infants. For example, the cost estimates were stratified per month for infants <1 year of age, resulting in costs per pertussis case aged 0 to 11 months ranging from €660 (\$900) to €7060 (\$9900) per case versus an overall cost of €3572 (\$5000) per infant case reported by de Greeff et al.

Sensitivity analysis showed that assumptions on vaccine price, transmission from parents to infants, and QALY losses had almost no impact on the results for the 3 immunization strategies. However, the ICER appeared to be sensitive to the values for vaccine effectiveness and underreporting. Decreasing the total pertussis incidence to 0.35% in adults, as reported by Ward et al²² in the United States, resulted in ICERs of €43,400 (\$60,800)/QALY and €28,000 (\$39,200)/QALY for cocooning and maternal immunization, respectively, from the payer's perspective. From the societal perspective, ICERs were €34,900 (\$48,900)/QALY and €24,800 (\$34,700)/QALY, respectively. The ICERs increased to €211,900 (\$296,700)/QALY and €81,600 (\$114,200)/QALY for cocooning and maternal immunization, respectively, when unreported cases were not taken into account in the analysis.

In the base-case analysis, the number of symptomatic pertussis cases was 200-fold higher than that reported by de Vries and Postma⁵¹ for the period 1996 to 2000. It was assumed that for the period 2002 to 2005, symptomatic pertussis would also be 200-fold higher than reported. By using this underreporting factor, it was estimated that the incidence of symptomatic pertussis in adults 25 to 34 years of age was ~3.5% annually. Recently, Nooitgedagt et al⁴⁰ reported an annual incidence of symptomatic pertussis of ~1.5% (95% CI, 1.1%–4.3%) among pregnant women in the Netherlands, which was lower than the estimates in this study. However, this study was not designed to obtain incidence data, and the results should be interpreted with caution because of the small sample size, inclusion bias, missing sample data, and annual fluctuations in incidence data. The sensitivity analysis with this model found that decreasing the underreporting factor by 80% to 90% still resulted in ICERs below the informal Dutch threshold (€20,000 [\$28,000]/QALY) for cocooning and maternal immunization.

Although uncertainty exists regarding the incidence of symptomatic pertussis, significantly lower incidence data still resulted in favorable ICERs. In the present study, a 20- to 30-fold increase in the incidence of reported cases resulted in ICERs below the informal Dutch threshold (€20,000 [\$28,000]/QALY) for cocooning and maternal immunization. Even lower ICERs could be obtained if medical costs for unreported symptomatic cases had been included in the analysis. However, this was not possible because of the lack of data. Furthermore, due to the lack of data, QALY losses for these

unreported symptomatic cases might have been too conservative.

Maternal immunization appeared to be the most effective strategy for protecting infants. This strategy might prevent ~1.5 times more infant pertussis cases than the cocooning strategy. This is mainly due to the assumption about effectiveness conferred by maternally acquired antibodies from birth until the infant is vaccinated within the current Dutch national immunization program. Although no clinical data on the effectiveness and tolerability of maternal immunization are yet available, several studies have reported that placental transfer of antibodies against pertussis may be effective.^{40,41} Currently, 2 registered clinical trials have begun recruiting participants for testing maternal immunization with acellular pertussis vaccines.⁶⁸

Decreasing the effectiveness of maternal antibodies from 89% to 70% resulted in a slight increase in the ICER (from €3500 [\$4900]/QALY to €3600 [\$5000]/QALY). The main disadvantage of maternal immunization was the rapid decrease in antibody titers after vaccination. Therefore, it was assumed that mothers should be vaccinated during every pregnancy to protect infants with maternally acquired antibodies. However, little is known about the tolerability of short-interval (eg, ~2-year) booster immunization at older age. Furthermore, it was assumed that maternal antibodies (in combination with routine infant vaccination) would provide a high level of protection during the first 4 months of life (89% effectiveness). With an alternative and more conservative assumption, limiting protection with maternal antibodies to 2 months would increase the cost-effectiveness ratios almost to the level reported for cocooning.

Implementation of the cocooning strategy would not provide full protection for newborns. Indeed, transmission from the mother in the first 2 weeks of the infant's life might not be prevented because of the delay in vaccine-induced immunity. The newborn would still be susceptible to other infectious sources, such as grandparents and other visitors. However, this strategy was the only one of the analyzed strategies that currently could be implemented because no vaccine has yet been approved for use in newborns or pregnant women. It also offers other advantages, such as indirect protection to contacts outside the family (both children and adults). This herd-immunity effect, which also may play a role in the other strategies, is not taken into account in this static model. It was believed that investigating the

strategies using a static model would be a conservative approach. It is not clear to what extent herd immunity would affect the results of this study. Further work should be directed toward developing a dynamic model, explicitly taking herd immunity into account.

For the cocooning strategy, it was assumed that the father would be vaccinated during the pregnancy and the mother would be vaccinated immediately after delivery. However, when it is safe to vaccinate women in the third trimester of the pregnancy, a combination of cocooning and maternal immunization (eg, vaccination of both parents during the pregnancy) can be considered. The main advantages of this combined strategy are that the infant is protected by maternally acquired antibodies and the risk from the 2 main sources of infection (the father and the mother) is eliminated. For this combined strategy, 181 infant pertussis cases might be prevented; from a payer's perspective, an ICER of €4400 [\$6200]/QALY was estimated and the highest overall QALY gain was found.

Finally, although immunization at birth seemed to be the most straightforward approach because the most vulnerable group would be vaccinated, the ICER of this strategy was higher than that of cocooning or maternal immunization. Because no data were available on underreporting of pertussis among infants (and it is unlikely that such data exist), it was assumed that no underreporting occurred in this age group, whereas in adults, underreporting (200-fold) was included in the analysis. The inclusion of underreporting in infants did result in a more favorable ICER for at-birth immunization. The exclusion of underreporting in older age groups resulted in ICERs far above the Dutch informal cost-effectiveness threshold. However, the present study found that both of the adult immunization strategies prevented more infant cases of pertussis than did immunization at birth, mainly due to the limited vaccine effectiveness assumed after administration of the first and second doses for immunization at birth. Therefore, cocooning and maternal immunization appeared to be the most effective strategies in preventing pertussis in unvaccinated or partly vaccinated infants.

The estimated ICERs of cocooning and maternal immunization were both generally robust in the sensitivity analysis. Only underreporting appeared to be crucial in this sense. Further research should be directed at underreporting, vaccine effectiveness, tolerability, and herd immunity within a dynamic-model context, all enabling more precise estimates of cost-effectiveness.

The present study did not include costs and QALY losses due to adverse events of vaccination. Because the adverse events associated with pertussis vaccination are generally mild, no serious QALY losses or costs would be expected. However, although these adverse events are rare, in the case of population-based vaccination programs, the total costs and QALY losses in the population due to adverse events might be substantial. Including the QALY losses and costs of adverse events might slightly increase the estimated ICERs of the analyzed immunization strategies.

Finally, this study took into account only the benefits of a reduced incidence of pertussis. However, because combination vaccines containing acellular pertussis as only one element are available for adults, additional benefits might be expected if combinations were used. Use of combination vaccines would be consistent with general recommendations on booster vaccinations against tetanus and specific recommendations for travelers (eg, diphtheria). Including additional benefits (eg, preventing other diseases in adults) will further improve the estimated ICERs of the cocooning and maternal immunization strategies. Alternatively, one could argue that only the marginal price of the pertussis component of the combination vaccine should be used in an analysis such as this one, which would improve the estimated ICERs.

CONCLUSIONS

This study estimated that both cocooning and maternal immunization were cost-effective (and even cost-saving) interventions that might be added to the current Dutch national immunization program. These estimates were mainly due to reductions in cases among the parents, which likely would not be severe and therefore would remain unreported. Immunization at birth was not cost-effective. Cocooning was the most expensive intervention to implement; however, it resulted in the highest number of QALYs gained (mainly in adults). Maternal immunization would offer better protection of infants, due to maternally acquired antibodies.

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and manuscript review; Mr. Sauboin = study design, data analysis and interpretation, and manuscript review; Dr. Postma = supervision, study design, data analysis and interpretation, and manuscript writing and review.

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